INSULIN STIMULATES HEART GLUCOSE UPTAKE IN VIVO BY INCREASING THE SARCOLEMMA GLUCOSE TRANSPORT VMAX

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Insulin (I) may affect net heart glucose (G) uptake in vivo both directly (acting on glycogen synthase, G transport, or glycolysis) and indirectly (lowering FFA). To assess the effect of I in vivo on G transport, we measured G transport by sarcolemma membrane vesicles from hearts of control (n=7) and I infused (2mU/min/kg x 2 hr, euglycemic insulin clamp, n=7) anaesthetized dogs. I's effects on both transport and in vivo net heart G (artery-coronary sinus) uptake were compared. In vivo, raising I (11±2 to 103±11 uU/ml) increased net G uptake 1.8-fold (0.48±0.08 vs 0.85±0.05 mM p<0.001) while plasma G remained constant 5.9±0.1 mM. In sarcolemma membranes (60-fold enriched for Na+K+ATPase), hyperinsulinemia increased stereospecific D-glucose uptake 1.8-fold (2.1±0.05 to 3.7±0.03 nmol/mg protein/min, p<0.02) at [G]=5mM. Over the [G] range between 0.1 and 20 mM, the Vmax increased 1.7-fold (5.9±3.8 to 9.9±1.8 nmol/min/mg) with no change in Km (9.0 vs 9.2 mM).
Conclusions: Physiologic increases in plasma I proportionately increase in vivo myocardial G uptake and the activity of sarcolemma G transport. This was due to a change in transporter capacity not substrate affinity. The close correspondence between changes in G uptake in vivo and transport in vitro suggests that in the heart, G transport may be rate limiting for G utilization in vivo even during hyperinsulinemia.

DETERIORATED CONTRACTILITY AND DISTURBANCE OF THE MYOCARDIAL ENERGY METABOLISM IN A.CA/SNJ MICE FOLLOWING IMMUNISATION WITH THE ADP/ATP CARRIER

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In previous studies we identified the ADP/ATP carrier as an autoantigen in human myocarditis and dilated cardiomyopathy. We also showed that autoantibodies to the ADP/ATP carrier inhibit the nucleotide transport in vitro. To examine the significance of these autoantibodies with regard to myocardial function and the intracellular energy metabolism, we immunized 20 A.CA/SnJ mice with purified carrier protein. After 4 months organspecific autoantibodies against the ADP/ATP carrier could be detected (ELISA) in 90% of the sera. Hemodynamic results obtained by Langendorff perfusion using an intraventricular balloon showed a remarkable reduction of contraction velocity. In 50% of the mice with a positive antibody titer cytosolic concentration of high energy phosphates was significantly reduced (ATP/ADP_{cyt} 6.5 vs. 19.9), mitochondrial concentration was increased (ATP/ADP_{mit} 1.9 vs. 1.4), as measured by non-aqueous fractionation. This constitutes a reduction of the cytosolic-mitochondrial phosphorylation potential difference of about 50% in the immunized animals. These findings suggest a possible pathophysiological role of antibodies against the ADP/ATP carrier in autoimmune myocarditis resulting in disturbance of the intracellular energy metabolism combined with an impairment of cardiac performance.

EVIDENCE FOR ACCELERATED GLYCOGENOLYSIS IN EARLY HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

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Changes in energy metabolism related to reduced myocardial blood supply have been demonstrated in established hypertensive left ventricular hypertrophy. It is not known if cardiac energy metabolism is shifted toward anaerobic pathways in early stages of hypertensive left ventricular hypertrophy. Accordingly, systolic arterial pressure (AP) [mmHg], LV/body weight (BW) [mg/g], glycogen and lactate levels (µmol/g tissue) from LV homogenate were measured in 8-week old SHR and normotensive Wistar-Kyoto (WKY) rats. Results ($\bar{x}$ ± SEM) are given below:

	WKY n=7	SHR n=6	p-val ≤
AP	132.00±2.42	183.67±7.52	0.001
LV/BW	2.40±0.09	2.66±0.09	0.07
Glycogen	19.14±1.37	15.43±0.67	0.05
Lactate	3.30±0.13	3.58±0.17	0.05

CONCLUSION:
Anaerobic glycogenolysis is accelerated during the early developmental stage of left ventricular hypertrophy in the young hypertensive rat; this alteration occurs before the development of severe left ventricular hypertrophy. These data underscore the need for aggressive early treatment of hypertension in young patients to minimize (and, possibly, prevent) the development of left ventricular hypertrophy.

ANGIOPLASTY PRODUCES MARKED AND PERSISTENT IMPAIRMENT OF VASCULAR CONTRACTILITY.

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Whether angioplasty (PTA) causes increased susceptibility to vasospasm or "stunning" of arterial smooth muscle is unclear. In order to elucidate the effect of PTA on control of vasomotor tone we examined the ability of smooth muscle to contract and relax following balloon dilation.

Atherosclerosis was induced in New Zealand rabbits (N=9) using a 0.5% cholesterol (C) diet and endothelial denudation of the right iliac artery and aorta. PTA of the right iliac artery was performed 6-8 weeks later using a 2.5 mm PTA balloon. The animals were sacrificed 1 to 8 weeks post-PTA. Segments (N=20 rings) from the right (C + PTA) and left (C alone) iliac arteries were assessed for in vitro smooth muscle contraction using potassium chloride (KCl) and phenylephrine (PE). Endothelial-dependent and -independent relaxation were tested for using acetylcholine (ACh) and nitroglycerin (NTG) respectively on pre-contracted segments.

	C Alone	C + PTA	P
Contraction (gm tension/mm² tissue, mean ± SEM)			
KCl	12.0 ± 1.4	3.2 ± 0.4	<0.001
PE	29.3 ± 4.2	4.7 ± 0.7	<0.001
Relaxation (% maximum contraction, mean ± SEM)			
ACh	26.7 ± 5.1	1.6 ± 5.0	<0.005
NTG	38.3 ± 5.5	38.6 ± 4.7	NS

We conclude that PTA in atherosclerotic rabbits results in marked impairment of vascular contractility and endothelial dependent relaxation. No improvement over time from PTA was observed. These findings tend to refute the hypothesis of increased susceptibility to vasospasm post-PTA.